Secretin: a physiological regulator of gastric emptying and acid output in dogs

Reference #1

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Division of Gastroenterology and Hepatology, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642; and Laboratory of Gastrointestinal and Liver Studies, Digestive Diseases Division, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799

Jin, H.-O., K. Y. Lee, T.-M. Chang, W. Y. Chey, and A. Dubois. Secretin: a physiological regulator of gastric emptying and acid output in dogs. *Am. J. Physiol.* 267 (*Gastrointest. Liver Physiol.* 30): G702–G708, 1994.—Secretin has been known to inhibit gastric acid secretion in several species. However, the physiological role of secretin on the postprandial acid output and gastric emptying in an intact stomach remains controversial. In the present study, we reinvestigated the role of secretin in physiological dose range and endogenous secretin on gastric acid secretion and emptying in the stomach without influencing intragastric luminal pH in dogs. In seven conscious dogs with gastric cannulas, a 4% amino acid meal was administered intragastrically, and three different doses of secretin and an antisecretin serum were infused intravenously in each dog on separate days. Gastric emptying and net acid output were measured using a dye dilution technique, and plasma secretin and gastrin were determined by specific radioimmunoassays. After the meal, gastric emptying was exponential: acid output peaked at 25 min, and plasma concentrations of gastrin and secretin peaked at 15 and 60 min, respectively. Intravenous infusion of secretin at 1.25, 2.5, and 5.0 pmol·kg^{-1}·h^{-1} dose dependently increased plasma levels of the peptide and suppressed postprandial plasma gastrin response and gastric acid output and emptying of the meal. Immunoneutralization of circulating secretin with a rabbit antisecretin serum abolished the postprandial rise of plasma secretin and significantly increased plasma gastrin, and augmented gastric emptying as well as acid output. It is concluded that, in dogs, secretin plays a physiological role in the regulation of gastric emptying and acid output after a liquid amino acid meal and that these effects may be mediated in part by suppression of the release of gastrin.

gastric acid secretion; antisecretin serum; gastrin; dye dilution technique

EXOGENOUS SECRETIN, in both pharmacological and physiological dose ranges, has been shown to inhibit gastric acid output and/or gastric emptying in humans, dogs, and rats (2–4, 8, 22, 32, 33). Because a specific secretin antagonist is not currently available for in vivo experiments, the only technique allowing determination of a physiological role of endogenous secretin has been in vivo immunoneutralization. In dogs, immunoneutralization of circulating secretin with a rabbit antisecretin serum increased postprandial acid output from a vagally innervated gastric pouch (4). However, the role of endogenous secretin in the regulation of postcibal acid output and gastric emptying in an intact stomach remains unclear. Furthermore, the mechanism through which secretin inhibits gastric emptying and acid output is unknown. Exogenous secretin inhibits postprandial gastrin release (22), and gastrin stimulates acid output and inhibits gastric emptying (15–17). Therefore, the effect of endogenous secretin on gastric function could be mediated in part through modulation of gastrin release.

The objectives of the present study were twofold: *1*) to investigate the physiological role of secretin on gastric emptying of a nutrient liquid meal and on the concurrent acid secretion stimulated by the meal in an intact stomach without interfering with intragastric pH or pressure, and *2*) to evaluate possible involvement of gastrin in secretin-induced suppression of gastric emptying and acid output.

MATERIALS AND METHODS

Animal preparation. Seven adult mongrel dogs weighing 15–20 kg were operated on under general anesthesia and were prepared with gastric cannulas, which were positioned in the most dependent portion of the stomach. Three weeks were allowed for recovery before studies began. Each animal was evaluated once a week, and a steady body weight was maintained throughout the study period. After an overnight 18-h fast with free access to water, the dogs were placed on Pavlov stands, and the gastric cannulas were opened and washed gently with warm water until clear fluids were obtained. Studies were started 10 min after introducing a 14-Fr Foley catheter into the stomach through the gastric cannula.

An intracatheter was inserted in each of two leg veins. One was kept patent by a slow infusion of 0.15 M NaCl solution for drawing blood samples, and the other was used for infusion of peptides and drugs.

Technique for measurement of gastric function. Gastric emptying and net acid output were determined concurrently using a previously validated dye dilution technique (11, 12, 14, 15). Briefly, 2.5 ml of fasting gastric content was aspirated as *sample 1*. Immediately thereafter, 5 ml of phenol red solution (200 mg/l, pH 7.5) was injected into the stomach and mixed with gastric fluids for 1 min. Another 2.5 ml of gastric contents was then aspirated as *sample 2* (double-sampling technique).

A 200 ml, 4% amino acid meal (Travasol, Baxter Healthcare, Deerfield, IL, 440 mosM) at pH 5.4 and containing phenol red (30 mg/l) was then instilled into the stomach over a 2.5-min period with a constant-infusion pump (Multi-speed Transmission, Harvard Apparatus, Dover, MA). Immediately after the meal infusion, 10 ml of gastric contents (*sample 3*) were aspirated and 20 ml of phenol red solution were injected into the stomach and mixed with the gastric contents as described above, and another 10 ml of gastric contents (*sample 4*) was obtained. The double sampling was repeated 5 min later and subsequently at 10-min intervals for 60 min.

A fraction of each sample of gastric contents and of the phenol red solutions was adjusted to pH 11.0 with 0.3% Na_3PO_4, and concentration of phenol red was determined at 560 nm (Microsample Spectrophotometer 300 N, Gilford, Oberlin, OH). Hydrogen ion concentration was determined by

titration with 0.01 N NaOH to an end point of pH 7.4 using a computer-aided titrimeter (Fischer Scientific, Pittsburgh, PA).

Experimental protocols. The amino acid meal was given 30 min after the start of a continuous intravenous infusion of one of the following treatments in each dog: *1*) 0.15 M NaCl containing 0.5% dog albumin at a rate of 30 ml/h; *2*) synthetic porcine secretin (a gift from Dr. David Coy, Tulane Univ.) dissolved in saline solution containing 0.5% dog albumin at doses of 1.25, 2.5, or 5.0 pmol·kg^{-1}·h^{-1}, given on separate days; and *3*) rabbit antisecretin serum (R7–5, 1.5 ml, iv bolus 15 min before meal).

Antisecretin serum R7–5 has an affinity constant of 1.4 × 10^{11} M^{-1} and a secretin binding site concentration of 18.9 μM. Similar to the antiserum used for radioimmunoassay, it was specific for secretin and has no cross-reaction with any other natural gut peptides including porcine cholecystokinin (CCK-33 or CCK-8), porcine motilin, and synthetic peptides including rat or human pancreatic polypeptide, somatostatin-14, peptide histidine-isoleucine amide, rat growth hormone-releasing factor, human glucagon-like peptide I, pituitary adenylate cyclase-activating peptide-(1—27), bovine glucagon, and porcine gastric inhibitory polypeptide. Natural porcine vasoactive intestinal peptide (VIP) cross-reacted at 0.2%, which could be due to contamination of a small amount of secretin, since synthetic VIP did not exhibit any cross-reaction. Rat secretin was equally reactive as porcine secretin, whereas chicken secretin was totally inactive. The synthetic porcine secretin fragment [Sec-(4—27)] cross-reacted at a potency of 62% of secretin, whereas the fragment Sec-(1—23) cross-reacted at 0.8%. Since both fragments could completely displace tracer binding, the antiserum appeared to be specific for the COOH-terminal region but required the presence of the NH_2-terminal region of secretin for maximum reactivity.

Radioimmunoassay of secretin and gastrin. Plasma concentration of secretin and gastrin was determined by radioimmunoassay as described previously (5, 29). Assay of antisecretin antibody in plasma was performed as described previously (5).

Measurement of bile acid in gastric contents. To rule out the possible contribution of duodenogastric reflux to the neutralization of gastric acid by intravenous infusion of secretin, bile acids in the gastric samples in both control and secretin-treated groups were assayed using an enzymatic assay kit consisting of 3α-hydroxysteroid dehydrogenase and diaphorase-coupled reactions (Sigma Diagnostics, St. Louis, MO) (30).

Analysis of data. Gastric emptying (as % of meal remaining in stomach over time) and net acid output (meq/10 min and meq/30 min) were calculated using a computer program (12, 14, 15) implemented on a personal computer (13). The percentage of meal remaining in the stomach was also expressed as the integrated area under the curve during the first and second 30-min postprandial periods (in % × 10 min). The fractional emptying rate (i.e., slope of decline of the % of meal remaining in stomach over time), the average intragastric acid concentration, and the rate of acid emptying were also calculated during each 10-min interval. All values were expressed as means ± SE. Statistical significance between the repeated measurements was determined by using two-way analysis of variance followed by Tukey's multiple comparison test. Correlation between gastric parameters and plasma levels of peptides was also determined using the Pearson correlation coefficient (18, 28). In addition, because plasma secretin levels, gastric emptying, and acid secretion were expressed in two 30-min periods (0–30, 31–60 min) in Tables 1–3, the integrated plasma secretin concentration (pM/30 min) and integrated duodenal acid load (meq/30 min) during these two 30-min periods were determined using the Pearson correlation coefficient. $P < 0.05$ is considered statistically significant.

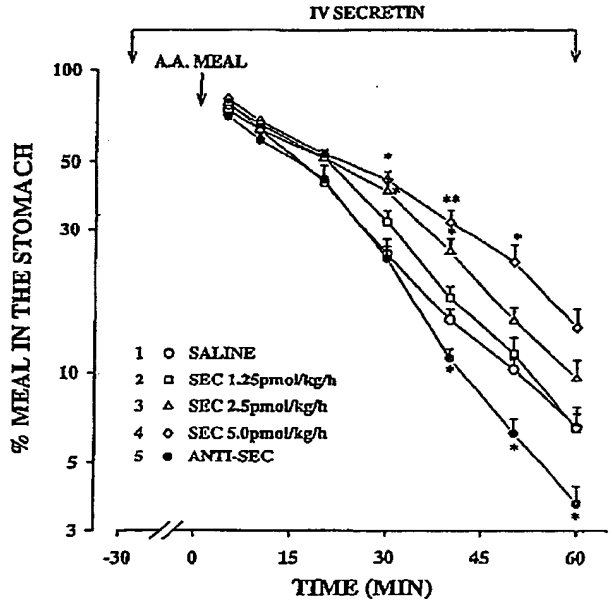

Fig. 1. Effect of exogenous secretin on gastric emptying of a liquid meal. Each point represents mean ± SE % of meal remaining in the stomach at each 10-min interval (n = 7). A. A. meal, amino acid meal. Meal was preceded by intravenous infusion of one of the following: *1*) saline, *2*) 1.25 pmol·kg^{-1}·h^{-1} secretin, *3*) 2.5 pmol·kg^{-1}·h^{-1} secretin, *4*) 5.0 pmol·kg^{-1}·h^{-1} secretin, and *5*) rabbit antisecretin (Anti-S) serum. *$P < 0.05$, **$P < 0.01$ compared with saline infusion.

RESULTS

Effects of a meal and of exogenous secretin. After 200 ml of 4% amino acid meal, gastric emptying was exponential, and continuous intravenous infusion of secretin significantly and dose dependently inhibited gastric emptying of this liquid meal (Fig. 1 and Table 1).

Net acid output increased postprandially to peak at 25 min (2.9 ± 0.2 meq/10 min) and then gradually decreased (Fig. 2 and Table 2). Secretin at 2.5 and 5.0 pmol·kg^{-1}·h^{-1}, but not 1.25 pmol·kg^{-1}·h^{-1}, significantly inhibited postprandial gastric acid output. While secretin was infused at 2.5 and 5.0 pmol·kg^{-1}·h^{-1}, the average acid output was 0.87 ± 0.13 and 0.76 ± 0.07 meq/10 min during the first 30-min interval after the meal, respectively, compared with 1.60 ± 0.13 meq/10 min during 0.15 M NaCl infusion (Table 2; $P < 0.01$). In addition, only the 5 pmol·kg^{-1}·h^{-1} dose significantly decreased acid output during the second 30-min interval after the meal (Fig. 2 and Table 2). There was a slightly increased concentration of bile acid in the gastric juice

Table 1. *Integrated percentage of meal remaining in the stomach (in % × 10 min)*

Treatment	0–30 min	31–60 min
Saline	339 ± 10	106 ± 9
Secretin, 1.25 pmol·kg^{-1}·h^{-1}	397 ± 16*	119 ± 12
Secretin, 2.5 pmol·kg^{-1}·h^{-1}	417 ± 21†	159 ± 14*
Secretin, 5 pmol·kg^{-1}·h^{-1}	446 ± 16†	281 ± 27†
Secretin antibody	335 ± 25	73 ± 6*

*$P < 0.05$, †$P < 0.01$ compared with saline.

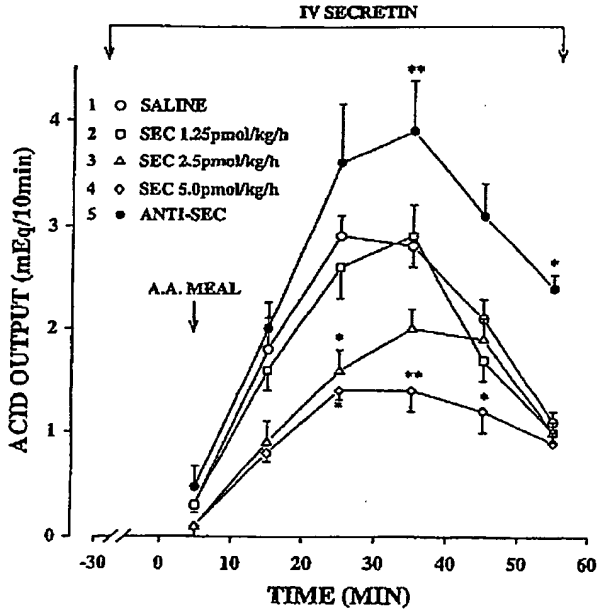

Fig. 2. Effects of exogenous secretin on gastric acid output stimulated by an amino acid meal. Each point represents mean ± SE acid output during each 10-min interval ($n = 7$). Meal was preceded by intravenous infusion of one of the following: *1*) saline, *2*) 1.25 pmol·kg^{-1}·h^{-1} secretin, *3*) 2.5 pmol·kg^{-1}·h^{-1} secretin, *4*) 5.0 pmol·kg^{-1}·h^{-1} secretin, and *5*) rabbit antisecretin (Anti-S) serum. *$P < 0.05$, **$P < 0.01$ compared with saline infusion.

postprandially. However, no difference was found in the bile acid concentration in gastric juice between the secretin-treated group and saline-treated group (data not shown), indicating that the duodenogastric reflux did not contribute significantly to the inhibitory effect of secretin on gastric acid secretion.

The combination of stimulated gastric acid output and gastric emptying of the amino acid meal modified the composition of the gastric contents, which resulted in progressively rising intragastric concentrations of acid during the postprandial period (Fig. 3). Following exogenous secretin, suppression of both gastric emptying and acid output was accompanied by a significant decrease of intragastric acid concentration (Fig. 3). Similarly, the rate of acid emptying was decreased by secretin; following immunoneutralization with the antiserum, it increased.

After the meal, plasma secretin increased significantly compared with basal at 45 min (1.6 ± 0.3 vs. 5.2 ± 1.0 pM), i.e., 30 min after the increase in acid output began; reached a peak of 11.4 ± 1.2 pM at 60 min, i.e., 30 min after the peak of acid output; and then gradually decreased (Fig. 4). Increasing doses of secretin produced proportionately higher plasma secretin levels, but only the 5 pmol·kg^{-1}·h^{-1} dose produced a peak level similar to that observed after the meal alone. The integrated secretin response also increased dose dependently, and these concentrations were significantly higher following exogenous secretin than after saline from 10 to 30 min, but not 30 to 60 min, after the meal (Table 3). Plasma secretin was inversely correlated with fractional emptying rate ($r = -0.627$; $P < 0.01$) and with acid output ($r = -0.420$; $P < 0.01$) and directly correlated with intragastric acid concentration ($r = 0.389$, $P < 0.01$) and the duodenal acid load ($r = 0.374$; $P < 0.03$). In addition, integrated plasma secretin was directly correlated with integrated duodenal acid load during the two 30-min periods ($r = 0.485$; $P < 0.001$) (Fig. 5).

Plasma gastrin level increased significantly from 15 to 30 min after the meal compared with fasting and then rapidly decreased from 45 to 90 min (Fig. 6), i.e., at the time when plasma secretin became elevated. Intravenous infusion of secretin decreased the postprandial gastrin response in a dose-dependent manner (Fig. 6). In addition, plasma secretin was inversely correlated with plasma gastrin ($r = -0.75$; $P < 0.0001$).

Effect of endogenous secretin. Immunoneutralization of circulating secretin with the antiserum completely abolished the postprandial rise of plasma secretin (Fig. 4). Plasma gastrin was significantly elevated compared

Table 2. *Effect of secretin and antisecretin serum on average gastric acid output (in meq × 10 min) stimulated by an amino acid meal*

Treatment	0–30 min	31–60 min
Saline	1.60 ± 0.13	2.00 ± 0.13
Secretin, 1.25 pmol·kg^{-1}·h^{-1}	1.53 ± 0.17	1.87 ± 0.17
Secretin, 2.5 pmol·kg^{-1}·h^{-1}	0.83 ± 0.13*	1.67 ± 0.13
Secretin, 5 pmol·kg^{-1}·h^{-1}	0.76 ± 0.07*	1.20 ± 0.13†
Secretin antibody	2.00 ± 0.30	3.20 ± 0.30*

*$P < 0.01$, †$P < 0.05$, compared with saline.

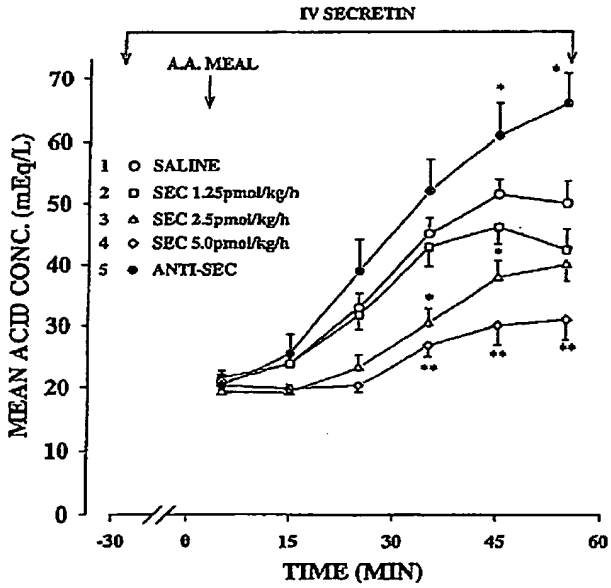

Fig. 3. Effects of exogenous secretin on intragastric acid concentrations after an amino acid meal. Each point represents mean ± SE acid concentration during each 10-min interval ($n = 7$). Meal was preceded by intravenous infusion of one the following: *1*) saline, *2*) 1.25 pmol·kg^{-1}·h^{-1} secretin, *3*) 2.5 pmol·kg^{-1}·h^{-1} secretin, *4*) 5.0 pmol·kg^{-1}·h^{-1} secretin, and *5*) 1.5 ml rabbit antisecretin (Anti-S) serum. *$P < 0.05$, **$P < 0.01$ compared with saline infusion.

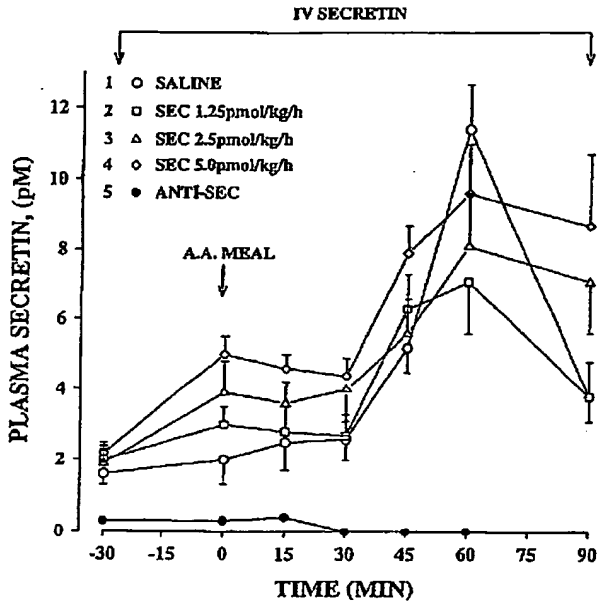

Fig. 4. Plasma concentration of secretin in response to an amino acid meal accompanied by intravenous administration of one of the following: *1*) saline, *2*) 1.25 pmol·kg^{-1}·h^{-1} secretin, *3*) 2.5 pmol·kg^{-1}·h^{-1} secretin, *4*) 5.0 pmol·kg^{-1}·h^{-1} secretin, and *5*) 1.5 ml rabbit anti-secretin (Anti-S) serum. Each point represents mean ± SE plasma level at each 15- or 30-min interval (n = 7).

with control immediately before the meal (42.7 ± 6.1 vs. 17.3 ± 1.9 pM; $P < 0.05$) (Fig. 6). After the meal, plasma gastrin was significantly ($P < 0.05$) greater than during saline at 30, 60, and 90 min (89.2 ± 12.9, 66.5 ± 11.0, and 51.0 ± 8.0 pM, respectively). Gastric emptying significantly increased during the second 30-min period, but not during the first 30 min after the meal (Fig. 1 and Table 1). Thus the integrated percentage of meal remaining in the stomach was reduced by 31% compared with the control group during the second 30-min postprandial period (Table 1; $P < 0.05$). Similarly, the anti-secretin serum injection increased acid output significantly compared with control only during the second 30-min postprandial period (2.00 ± 0.13 vs. 3.2 ± 0.30 meq/10 min, $P < 0.01$) (Fig. 2 and Table 2).

DISCUSSION

The results of the present study indicate that endogenous secretin plays a physiological role in the regulation of both gastric emptying and acid secretion after an amino acid liquid meal in dogs. First, we found that immunoneutralization of circulating secretin with the antisecretin serum completely abolished the rise in plasma secretin observed 30–60 min after the meal and significantly increased gastric emptying and acid output during that same time period. Importantly, immunoneutralization of endogenous secretin had no effect on gastric functions during the first 30 min after a caloric meal, i.e., when plasma secretin was not elevated compared with fasting, but only 30–60 min after the meal, i.e., at those times when plasma secretin was physiologically elevated. Because no specific secretin antagonist is currently available for in vivo experiment, this approach is the only method permitting the evaluation of the effect of the inhibition of endogenous secretin on gastric function. Second, we observed that exogenous secretin in physiological doses, 2.5 and 5.0 (but not 1.25) pmol·kg^{-1}·h^{-1}, significantly decreased gastric emptying, acid output, and intragastric concentration of acid after a caloric meal. This finding confirms the previous report that secretin infusion at 2.5 pmol·kg^{-1}·h^{-1} delays gastric emptying in humans, although a noncaloric saline meal was used and plasma secretin levels were not determined (32). Thus no other studies in the dog or in any other animal species have determined the effect of caloric meals on postprandial gastric function while measuring concurrently plasma secretin levels. Third, administration of these physiological doses of secretin before, during, and after the meal elevated the integrated plasma concentrations of secretin dose dependently, although these concentrations were not significantly higher following exogenous secretin than after saline from 30 to 60 min after the meal (Table 3). This

Table 3. *Integrated concentrations of secretin (in pM × 10 min) during each of the two 30-min periods*

Treatment	0–30 min	31–60 min
Saline	20.5 ± 2.5	83.0 ± 5.8
Secretin, 1.25 pmol·kg^{-1}·h^{-1}	27.5 ± 2.9*	66.0 ± 10.0
Secretin, 2.5 pmol·kg^{-1}·h^{-1}	38.0 ± 4.8*	69.7 ± 10.3
Secretin, 5 pmol·kg^{-1}·h^{-1}	46.0 ± 2.3†	87.4 ± 10.7
Secretin antibody	0.13 ± 0.003†	0.07 ± 0.003†

*$P < 0.05$, †$P < 0.01$ compared with saline.

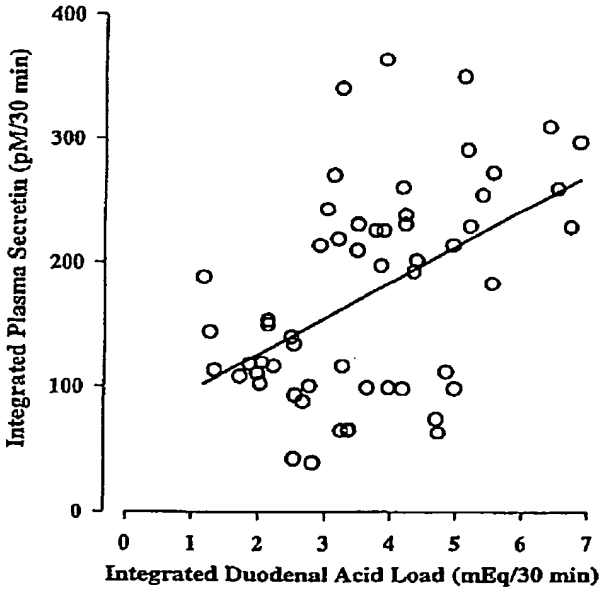

Fig. 5. Correlation between integrated plasma secretin concentration (pM/30 min) and integrated duodenal acid load (meq/30 min) during the two 30-min periods (integrated values were calculated during 0–30 and 31–60 min, respectively) (n = 7, total values = 56). Each circle represents the individual value (Y = 2.88X + 68.272, r = 0.485, $P < 0.01$).

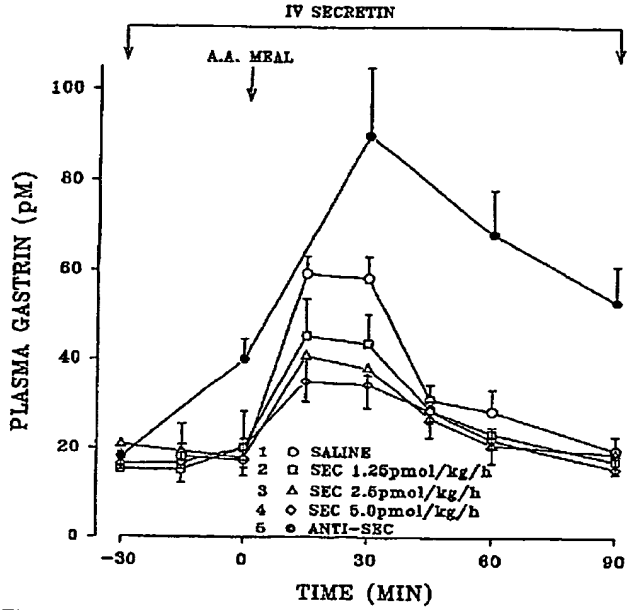

Fig. 6. Plasma concentration of gastrin in response to an amino acid meal accompanied by intravenous administration of one of the following: *1*) saline, *2*) 1.25 pmol·kg^{-1}·h^{-1} secretin, *3*) 2.5 pmol·kg^{-1}·h^{-1} secretin, *4*) 5.0 pmol·kg^{-1}·h^{-1} secretin, and *5*) 1.5 ml rabbit antisecretin (Anti-S) serum. Each point represents mean ± SE acid output during each 15- or 30-min interval (n = 7).

apparently surprising observation may be due to the fact that endogenous secretin release is known to depend on the presence of acid in the duodenum (7, 19, 21, 27). Thus a dose-dependent increase of plasma secretin from 0 to 30 min produced inhibition of gastric emptying, of intragastric acid concentration, and of acid output. In turn, the resultant reduction in duodenal acidity appears to have inhibited the later release of endogenous secretin, which may have masked the additional effect of exogenous secretin administration on plasma concentration of the peptide. This hypothesis is further supported by our finding that plasma secretin was inversely correlated with gastric emptying and with acid output, which confirms our previous observation (6), and directly correlated with intragastric acid concentration and in particular with the duodenal acid load.

The mechanism through which secretin inhibits gastric emptying remains unclear. In humans, pharmacological doses of secretin have been shown to reduce intragastric pressure and to induce contractions of the pylorus (26), thereby slowing gastric emptying. More recently, a physiological dose of secretin (2.5 pmol·kg^{-1}·h^{-1}) was shown to produce alterations of gastroduodenal motility that are known to be associated with delayed gastric emptying: contraction frequency was reduced in the antrum, pylorus, and duodenum during fasting (20), and the frequency and amplitude of contraction in both antrum and duodenum were reduced following a meal (9).

In addition to its role in the postprandial control of gastric emptying, secretin is believed to be involved in the regulation of acid output. Pharmacological doses of secretin are known to strongly inhibit gastric acid output (2, 3, 23, 25, 31). Physiological doses of secretin (5 pmol·kg^{-1}·h^{-1}) significantly decreased acid output stimulated by intravenous infusion of human synthetic gastrin in dogs prepared with vagally innervated fundic pouches (4). Also in dogs, intravenous administration of a rabbit antisecretin serum produced a significant augmentation of postprandial acid output (4) as well as postprandial gastrin release (22). In humans, secretin in a dose as small as 2.8 pmol·kg^{-1}·h^{-1} significantly suppressed gastric acid output stimulated by low dose of pentagastrin (80 pmol·kg^{-1}·h^{-1}) (33). In the present studies, we confirmed the inhibitory effect of the physiological role of secretin on acid secretion by both immunoneutralizing endogenous secretin with antisecretin serum and intravenous infusion of exogenous secretin. Furthermore, by analyzing bile acid concentration in the gastric juice, we ruled out a significant duodenogastric reflux, which might contribute to the inhibition of acid secretion. Therefore, it is more convincing to categorize secretin as a true enterogastrone. It was suggested recently that secretin releases somatostatin from cultured rat antral cells, which may be responsible for the inhibitory action on the parietal cells (1). Our recent observation in total isolated perfused rat stomach supports their observation (1) that secretin given intraarterially increases the somatostatin level in the portal venous effluent (I. S. Chung, P. Li, K. Y. Lee, T. M. Chang, and W. Y. Chey, unpublished data).

In contrast to the above observations, with use of the intragastric titration technique, physiological dose of secretin has been reported as failing to inhibit acid secretion and gastrin response to peptone meal (pH 5.5) in humans (24), although significant inhibitions occurred in both during peptone meals given at pH 2.5 or 2.0. However, unlike the postprandial state, during the intragastric titration of gastric contents to maintain pH 5.5 after peptone meal, plasma gastrin continuously remained at a rather high level because of a lack of normal feedback control of gastrin release by normal acid secretion. Therefore, physiological dose of secretin might not encounter the higher plasma gastrin level to exert the inhibitory effect of secretin on acid secretion, since we believe that the inhibitory effect of secretin on acid secretion is mediated, at least in part, by decreased release of gastrin. Indeed, in four of the seven dogs studied in the present study, when gastric acid secretion and gastrin release were maximally stimulated by the same amino acid meal using the intragastric titration technique (24), the physiological doses of secretin used in the present study, including 2.5 and 5.0 pmol·kg^{-1}·h^{-1}, could not influence either the increased acid output or plasma gastrin levels (unpublished data). Only when the dose of secretin was increased to 20 pmol·kg^{-1}·h^{-1} (at 4–8 times higher than physiological doses) could a significant inhibition of the acid secretion and gastrin release be achieved. More work needs to be done to clarify this issue.

In studies using the intragastric titration technique, maintaining postprandial intragastric pH to 2.5 or 5.5

elegantly demonstrated that intragastric pH modulates the acid output stimulated by intragastric peptone and that this effect appeared to be mediated by endogenous gastrin (16). In the present study, the inhibitory effect of endogenous and exogenous secretin on acid output was studied in a physiological context by using a dye dilution method that allows the normal fluctuations of intragastric pH to occur. By measuring concurrently gastric acid output, gastric emptying, plasma secretin, and plasma gastrin, we were able to evaluate the intricate relation between gastric function and these peptides. First, we observed that plasma secretin was not significantly elevated during the first 30 min after an amino acid meal, at the time when acid output and plasma gastrin reached a peak, and that plasma gastrin and acid output started to decrease at the time endogenous secretin started to increase, i.e., 45 min after the meal. In addition, there was a direct significant correlation between secretin levels and duodenal acid load. Thus the presence of an amino acid meal in the stomach and its emptying into the duodenum was accompanied by an immediate elevation of plasma gastrin. In contrast, the postprandial elevation of plasma secretin was delayed until after the pH of the gastric contents had been lowered by the meal-induced stimulation of acid output. This latter effect could result in part from the release of gastrin, which was observed during the first 30 min after the meal.

Following a continuous infusion of secretin at physiological doses (1.25 and 2.5 $pmol \cdot kg^{-1} \cdot h^{-1}$), plasma secretin levels increased twofold during the first 30 min after the meal, and plasma gastrin and acid output decreased by 50%. From 30 to 60 min after the meal, exogenous secretin did not further elevate plasma secretin compared with saline infusion; in fact, peak plasma secretin was reduced. Interestingly, this effect was incompletely counteracted by exogenous infusion of the peptide. During that same late postprandial period, a dose of 5 $pmol \cdot kg^{-1} \cdot h^{-1}$ produced peak plasma levels of secretin comparable to those observed after saline infusion while significantly suppressing acid output, but without modifying plasma gastrin. Finally, administration of an antisecretin serum was able to suppress the rise of endogenous secretin normally observed from 30 to 60 min and to concurrently increase both plasma gastrin and acid output. In our previous studies (4, 5, 22), a normal rabbit serum was shown to have little influence on the release of gastrin or gastric acid secretion or pancreatic bicarbonate secretion stimulated by a meat meal.

These results confirm the previous observation that secretin plays a significant role in the regulation of postprandial release of gastrin (22), and they further illustrate that the release of secretin after a meal depends on gastric acid delivered into the duodenum, as previously shown in dogs (6, 21) and humans (7, 19, 27). In addition, the results indicate that circulating secretin may be responsible, at least in part, for the late postprandial inhibition of acid output and that this effect could be mediated by endogenous gastrin. These findings also illustrate the robustness of the feedback mechanisms that are involved in peptide regulation of acid output and point to the need for precise and concurrent measurements of the various aspects of gastric function while studying peptide regulation of acid output.

In conclusion, secretin is a true enterogastrone that plays an important role in the regulation of gastric emptying, acid output, and plasma gastrin release after an amino acid meal in dogs. The effect on postprandial acid output may be mediated in part through inhibition of gastrin release.

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